UNIVERSITY OF THESSALY

SCHOOL OF MEDICINE LABORATORY OF BIOMATHEMATICS

M.SC. "RESEARCH METHODOLOGY IN BIOMEDICINE, BIOSTATISTICS AND CLINICAL BIOINFORMATICS"

MASTER'S THESIS

"ASSESSMENT OF REPORTING QUALITY OF META- ANALYSES IN TERLIPRESSIN IN HEPATORENAL SYNDROME PUBLISHED FROM 2010 TO 2018 USING PRISMA STATEMENT"

ANGELIKI TSAKOU, MD

" Αξιολόγηση της ποιότητας αναφοράς των μετα- αναλύσεων για την Τερλιπρεσσίνη στο Ηπατονεφρικό Σύνδρομο , που δημοσιεύτηκαν από 2010 έως το 2018 χρησιμοποιώντας το PRISMA statement "

Committee members:

Supervisor: Prof. Ioannis Stefanidis

Evaluator 1: Chrisoula Doxani, MSc, MD

Evaluator 2: Prof. Zintzaras Elias

Abstract

Background: Hepatorenal syndrome is a serious, potentially lethal complication of advanced cirrhosis. Different pharmacological therapies using vasoactive agents have been used to treat HSR. The most considered vasoconstrictor drug is Terlipressin. Many Systematic Reviews (SRs) and Meta-analyses (MAs) have been published addressing the efficacy of Terlipressin in comparison with other vasoactive agents.

Objective: The aim of this study is to assess the overall reporting quality of Systematic Reviews and Meta-analyses on Terlipressin in Hepatorenal Syndrome.

Methods: Five electronic databases were searched in August 2018 in order to locate all SRs and MAs that have been published from 2010 to 2018, reporting the efficacy of Terlipressin in HRS. The reporting quality of the included meta-analyses was evaluated based on the PRISMA statement. Total PRISMA scores and frequencies of reporting each item were calculated and univariate linear regression analyses were performed to explore potential factors that influence the reporting quality of the articles.

Results A total of 15 Meta-analyses were included. The results showed that the overall reporting quality was adequate, with mean PRISMA score = 21/27 (77 %). Ten items were 100% reported while Objectives (20%) and Protocol and Registration (26, 7%) were the items that had the poorest adherence. The 26, 6% of the MAs were published in PRISMA – endorsing journals with a median JIF = 4. Most studies had as primary outcomes HRS reversal and mortality. Terlipressin was in all MAs statistically superior to placebo or no intervention in the reversal of HRS. However, terlipressin was also associated with more Adverse Events than placebo.

Conclusions: The overall reporting quality of meta-analyses in Terlipressin in HRS was in general adequate. Objectives were the item having the poorest adherence. The main primary outcome of MAs was HRS reversal. Terlipressin was proved superior to Placebo considering HRS Reversal but was associated with more adverse events. To raise the reporting quality of meta-analyses on terlipressin in HRS, further, improvement is needed.

Keywords: PRISMA, Hepatorenal, Terlipressin, Systematic Review, Meta-analysis, reporting quality

Introduction

Hepatorenal syndrome (HRS) is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure. (1) It is a severe, potentially fatal complication of decompensated liver cirrhosis and its optimum treatment is Liver Transplantation.

The development of hepatorenal syndrome has been associated with the circulatory changes seen in cirrhosis of the liver subsequent to portal hypertension and vasodilation of the splanchnic arteries. (2) Portal hypertension and the vasodilation of the splanchnic arteries burden the cardiac effort and as a result, they reduce the cardiac output and systematic hypotension occurs. This systematic hypotension and peripheral vasoconstriction result in a reduction of the renal arterial perfusion. Consequently, renal homoeostatic mechanisms, such as the renin-angiotensin system, vasopressin, and the sympathetic nervous system, are overactive in order to maintain the renal arterial blood pressure.

The International Club of Ascites has developed diagnostic criteria of Hepatorenal Syndrome, which are universally accepted and followed (Table 1). These criteria confirm that Hepatorenal syndrome is a diagnosis of exclusion. There are clinically two distinct types of Hepatorenal Syndrome. Type 1 HRS is characterized by a rapidly progressive renal failure defined by a doubling of the initial serum creatinine to a level greater than 2.5 mg/dl or 220 μmol/l in less than 2 weeks. (3) This impairment is usually precipitated by an aggravating event, such as acute bacterial infection and a dysregulated systemic inflammatory response. Type-1 HRS is associated with very poor prognosis and if it is left untreated, it has a 2-week mortality rate of ≈ 80%. (1) Type-2 HRS is characterized by a moderate renal failure which follows a steady or slowly progressive course (serum creatinine greater than 1.5 mg/dl or 133 μmol/l). Patients with type-2 HRS have a better prognosis with median survival around 6 months without transplantation. (1)

Criteria for the diagnosis of Hepatorenal Syndrome – International Club of Ascites (ICA)
1. Presence of cirrhosis and ascites
2. Serum creatinine >1.5 mg/dL (or 133 micromoles/L)
3. No improvement of serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (recommended dose: 1 g/kg b.w. per day up to a maximum of 100 grams of albumin/day)
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. Absence of parenchymal kidney disease as indicated by : • proteinuria >500 mg/day • microhematuria (>50 RBCs/high power field) and/or • abnormal renal ultrasound scanning)

Table 1: Diagnostic Criteria of HRS - ICA

Pharmacological therapies of Hepatorenal Syndrome aim to alter the circulatory derangements seen in cirrhosis by inducing splanchnic and systematic vasoconstriction in conjunction with volume expansion. For this reason, vasoactive agents are used together with albumin. The mainly used and studied vasoactive agents are Terlipressin, Noradrenaline, Midodrine with octreotide and Dopamine with furosemide. Among these agents, the most studied one is Terlipressin, because although it is the most used one with proven efficacy, it is not worldwide approved which study the efficacy and safety of the vasoactive agents in HRS have been published the last decade. Therefore many Systematic Reviews and Meta-analyses, as well, have tried to evaluate these trials and their conclusions in order to reach to a final inference and maybe suggest general guidelines for the treatment of Hepatorenal syndrome.

Given the number of meta-analyses published the previous years and the fact that the aforementioned meta-analyses are often influential, the purpose of this study is to search the best currently available evidence systematically and evaluate the reporting quality of meta-analyses in Terlipressin in Hepatorenal Syndrome, published from 2010 to 2018, by using PRISMA statement..

Methods

Eligibility Criteria

To be eligible for inclusion, studies had to fulfill the following criteria:

1. Be described as “meta-analysis” or “systematic review” or both
2. The RCT’s studied to be on adult patients with HRS
3. Study therapeutic strategies including Terlipressin
4. Be published in English as a full text
5. Be published between 2010 and 2018

Literature Search

Using the aforementioned criteria, a comprehensive literature search was conducted during September 2018 using MEDLINE, PubMed, EMBASE (via Scopus), Web of Science, Cochrane Database of Systematic Reviews, NIM, AASLD, and EASL. Moreover, additional search in specific journals as Journal of Hepatology, Clinical Gastroenterology and Hepatology, Gut Journal and The Lancet Gastroenterology & Hepatology was conducted to identify relevant literature. Papers that were identified as review articles or pooled analysis were excluded. (4)

Data Extraction

A sensitivity search strategy was performed using the medical subject heading terms (MeSH) and keywords: “hepatorenal syndrome,” “terlipressin,” “vasoactive,” “vasoconstrictor,” “systematic review,” and “meta-analysis”. Titles and abstracts were at first evaluated based on the inclusion criteria and full texts of potentially eligible studies were retrieved. Furthermore, data referring to the year and journal of publication, number of trials included in the meta-analysis and the number of authors involved in the study were extracted.

Assessment of reporting quality and Data Analysis

Assessment of reporting quality and Data Analysis

The evaluation of the reporting quality of meta-analyses was performed based on PRISMA statement using as a tool the PRISMA checklist (Figure 1 & 2). This checklist is a questionnaire of 27 items divided into seven sections (Title, Abstract, Introduction, Methods, Results, Discussion, and Funding). The PRISMA authors have published a lengthy Explanation and Elaboration document, for a better understanding of the rationale and the content of each item. Meta-analyses were thoroughly reviewed in order to determine whether they fulfill each query or not. Some of the items on the checklist contain multiple components, so if most of them were met, the answer was “yes” and a score of 1 was assigned. Otherwise, the answer was considered as “no” and a score of 0 was assigned, as well. Thus, a total PRISMA score for each article was obtained with maximum probable total PRISMA score being equal to 27. This score was also expressed as frequency and proportion.

Data were analyzed by the statistical software SPSS (IBM SPSS Statistics 25.0) and descriptive analysis was performed for characteristics. A P-value of 0.05 was set as a threshold of statistical significance.(5) Pearson correlation “r” was used to detect a potential correlation between reporting quality and specific variables (e.g. JIF). Finally, forest plots were created to display the primary outcomes of the meta-analyses.

Results

Search Results

Through an electronic literature search, a total of 199 articles were initially identified. After omitting duplicates, 142 papers were screened and excluded on the basis of their Title and Abstract. The main reason for exclusion was the discrepancy with the

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Page 1 of 2

Figure 1: PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additiona analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Figure 2: PRISMA checklist

eligibility criteria in respect of content (not about Terlipressin). Then the remained full-text articles were assessed for inclusion, from which 69 were rejected according to our criteria. Most of them were excluded due to deviation with the defined timeline of the present paper. Figure 3 depicts a flow diagram of article inclusion. (6).

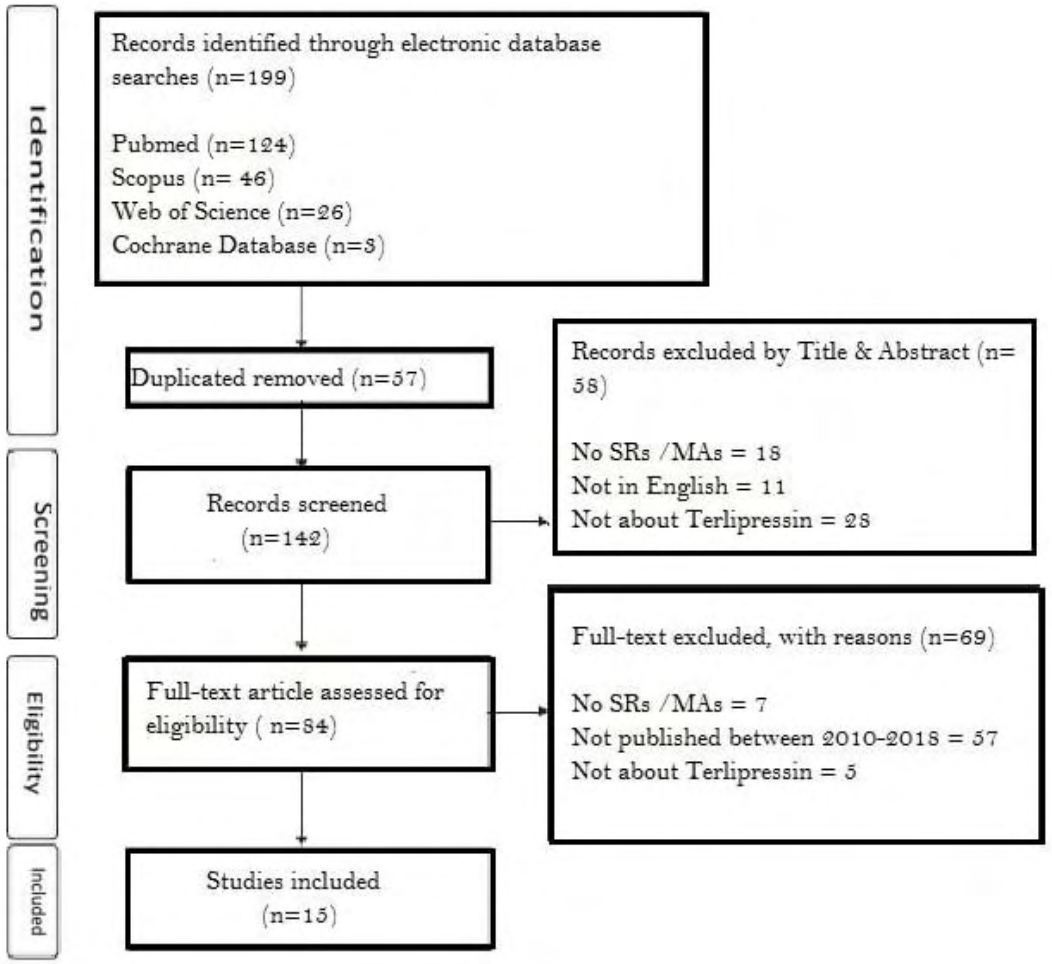

Figure 3: Flow Chart of the study selection progress

Review Characteristics

Table 2&3 and Bar charts 1 & 2 display the general characteristics of the included meta-analyses regarding year and journal of publication, number of authors, continent of origin, JIF, PRISMA endorsement, and funding. Table 3 summaries the descriptive analysis of Year of publication, Number of Authors and JIF. Most of the studies were published in 2017 (7/15, 46, 7%) (Chart 1). Journals of publication had a median JIF = 4 and a range from 0, 90 to 53, 2. The meta-analysis by Facciorusso et. Al was published in Lancet Gastroenterology & Hepatology which has the greater JIF= 53, 2. Only 26, 6% (4/15) of the journals of publication endorsed PRISMA statement. There was a mean = 4, 67 of authors per published meta-analysis, with 26, 7% having nAuthors =

4. (6). No continent of origin distinguished from the others, as seen in Table 4 and Bar Chart 2. Finally, only two of the included MAs declare Funding from an individual source.(3, 7-19)

Author	Year	Continent	n Authors	Journal	JIF	PRISMA Endorsement	Funding
Mattos	2016	South America	2	European Journal of Gastroenterology & Hepatology	2,014	No	-
Nassar Junior	2014	South America & Europe	5	PLOS ONE	2,766	Yes	No
Hiremath	2013	Asia	2	Indian Journal of Pharmacology	0,902	No	-
Israelsen	2017	Europe & N. America	7	The Cochrane Collaboration	6,124	No	No
Sagi	2010	North America	4	Journal of Gastroenterology & Hepatology	3.483	No	-
Wang	2017	Asia	5	Medicine	2,028	No	No
Gluud	2012	Europe	4	The Cochrane Collaboration	6,124	No	No
Dobre	2010	North America	4	Int Urol Nephrol	1,564	No	-
Facciorusso	2016	Europe & N. America	7	Lancet Gastroenterology & Hepatology	53,254	Yes	No
Gifford	2017	Europe	3	Alimentary Pharmacology & Therapeutics	7,357	Yes	Yes
Gluud	2010	Europe	4	Hepatology	14,079	No	-
Nanda	2017	North America	5	Journal of Clinical Gastroenterology	7,683	No	-
Zheng	2017	Asia	8	Expert Review of Gastroenterology & Hepatology	2,963	No	Yes
Allegretti	2017	Europe & N. America	8	The Cochrane Collaboration	6,124	No	No
Sridharan	2017	Oceania	2	JGIM	4,005	Yes	No

Table 2: General Study Characteristics

Statistics

		nAuthors	Year	JIF
N	Valid	15	15	15
	Missing	0	0	0
Mean		4,67	2014,67	8,0238
Median		4,00	2016,00	4,0000
Range		6	7	52,30
Minimum		2	2010	,90
Maximum		8	2017	53,20

Table 3: Descriptive Analysis of Year of publication, JIG and number of Authors

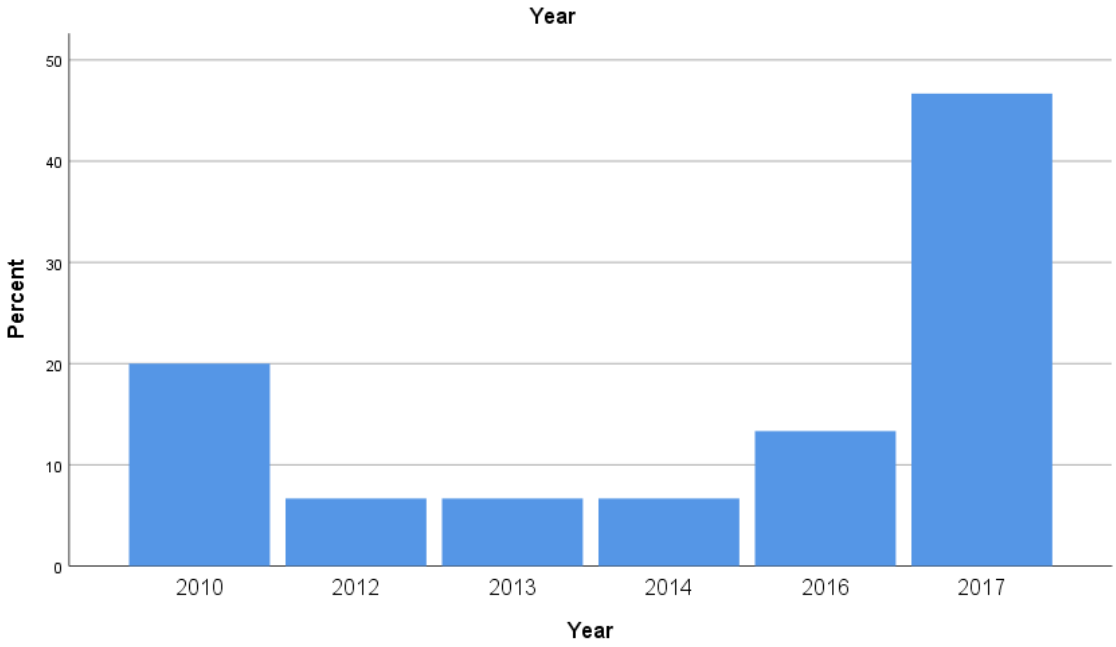

Chart 1: %Proportion of Year of Publication

Country

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Europe	3	20,0	20,0	20,0
	North America	3	20,0	20,0	40,0
	South America	1	6,7	6,7	46,7
	Asia	3	20,0	20,0	66,7
	Oceania	1	6,7	6,7	73,3
	Europe & N. America	3	20,0	20,0	93,3
	S. America & Europe	1	6,7	6,7	100,0
	Total	15	100,0	100,0	

Table 4: Frequency & proportion of Meta-analyses' Continent of Origin

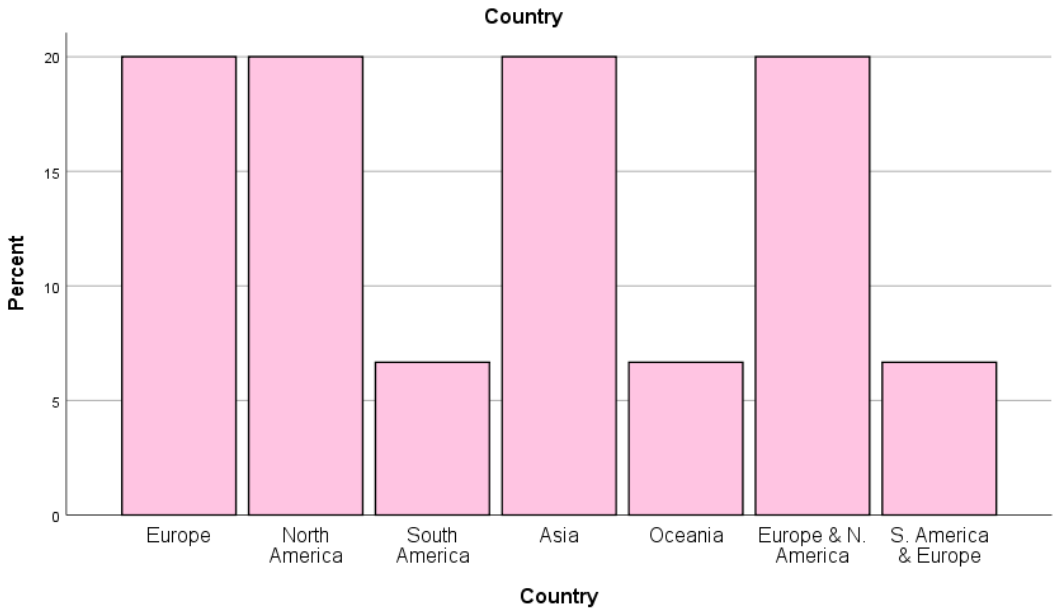

Chart 2: %Proportion of Continents of Origin

Table 5 depicts characteristics of meta-analyses regarding their content (e.g. number of trials, number of patients, intervention, and outcomes) and the quality of their included studies. Almost all of the meta-analyses studied exclusively RCT's, with Hiremath's meta-analysis being the exception (12) A median of n=10 RCT's was included in each meta-analysis, while 20% of them embody n=4 number of trials (Chart 3). The most common comparison was between Terlipressin and Placebo or Noradrenaline and the main primary outcomes were HRS Reversal and short-term Mortality. As for quality assessment, the Cochrane Risk of Bias Tool was used in 46, 6% (7/15) of meta-analyses. The rest of the MAs used other quality assessment tools as GRADE and Jadad Score. Finally, the majority (46, 6%) of the meta-analyses conclude that have been based on low quality- high risk RCT's. Only two meta-analyses (Wang & Gluud 2010) have declared high trial quality. (10, 19)

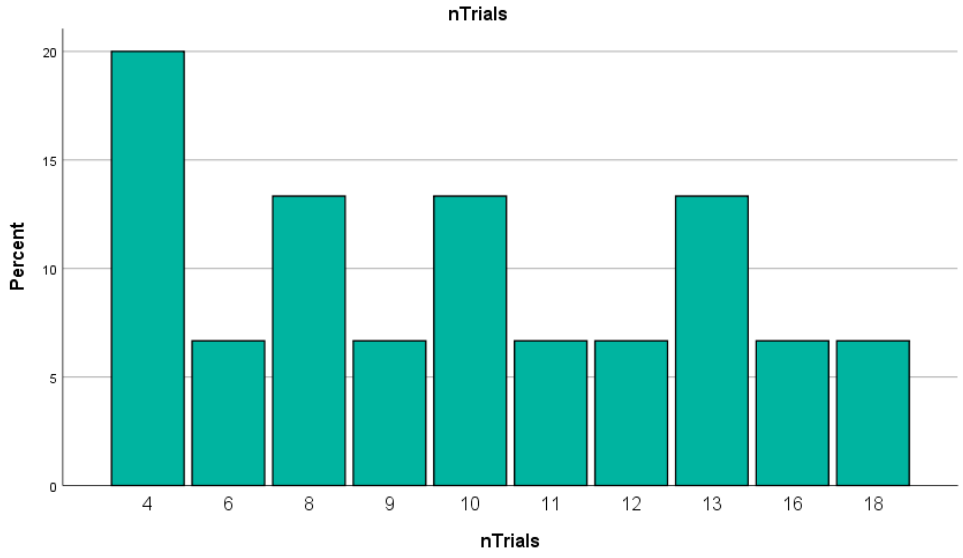

Chart 3: % Proportion of number of included trials

Author	Type Studies	n Trials	n Patients	Intervention	Primary Outcome	Secondary Outcome	Study Quality	Study Quality
Mattos	RCT's	4	154	Terlipressin Vs Noradrenaline	30-day Survival & Economic Evaluation	HRS Reversal	GRADE Working Group	Moderate Quality
Nassar Junior	RCT's	4	154	Terlipressin Vs Noradrenaline	HRS Reversal	Mortality Recurrence HRS & AE	Cochrane Risk of Bias Tool	High Risk
Hiremath	Any	8	377	Terlipressin Vs Placebo	Mortality	-	Nancy et al.	N/S
Israelsen	RCT's	10	474	Terlipressin Vs other Vasoactive drugs	Mortality - HRS Resistance & AE	Quality of life & no serious AE	Cochrane Risk of Bias Tool	High Risk
Sagi	RCT's	4	223 [1]	Terlipressin Vs Placebo	HRS Reversal	Recurrence HRS & Survival	Jadad score	Average Quality
Wang	RCT's	18	1011	Terlipressin Vs Placebo or Vasoactive	HRS Reversal & Mortality	Recurrence HRS & AE	Jadad score	High Quality
Gluud	RCT's	6	N/S*	Terlipressin Vs Placebo	Mortality - HRS Resistance & AE	-	Cochrane Risk of Bias Tool	Low Risk
Dobre	RCT's	8	320	Terlipressin Vs Placebo or Noradrenaline	HRS Reversal - MBP – Cr Serum – Urine output	Survival – AE	Cochrane Risk of Bias Tool	High Risk
Facciorusso	RCT's	13	739 [1]	Terlipressin Vs Placebo or Noradrenaline	30-day Mortality	HRS Reversal - AE	GRADE	Low – moderate Quality
Gifford	RCT's	12	700 [1]	Terlipressin Vs Placebo or Vasoactive	HRS Reversal – Mortality & AE	-	Cochrane Risk of Bias Tool	High Risk
Gluud	RCT's	10	376	Terlipressin Vs Placebo or Noradrenaline	Mortality	HRS Reversal – AE- Cr	Author's Judgement	Low Quality
Nanda	RCT's	13	770	Terlipressin Vs Placebo or Vasoactive	HRS Reversal	Recurrence HRS & Survival	Jadad score	Average Quality
Zheng	RCT's	11	685 [1]	Terlipressin Vs Placebo or Noradrenaline	HRS Reversal	Survival – AE	Cochrane Risk of Bias Tool	Moderate Risk
Allegretti	RCT's	9	534	Terlipressin Vs Placebo	Mortality - HRS Resistance & AE	-	Cochrane Risk of Bias Tool	High Risk
Sridharan	RCT's	16	762	Terlipressin Vs Placebo	HRS Reversal	Mortality - AE	GRADE	Very Low Quality

Table 5: Characteristics of Content & Quality of the included studies *N/S = not stated [1] = only HRS Type 1 population

Reporting Quality

The mean PRISMA score of the 15 eligible MAs was mean= 21 (SD= 2, 1) out of 27 and the mean adherence rate of all items to the checklist was 77, 7%. Therefore the overall quality of the meta-analyses can be described as moderate. None of the studies reported all of the items of PRISMA's checklist. Two meta-analyses had the greater PRISMA Score with Score = 24/27. These were Israelsen et al. (2017) & Sridharan et al. (2017 (13, 18). On the other hand, Sagi et al. (2010) meta-analysis succeeded the lowest PRISMA Score with a value of Score = 17/27 and then followed Zheng et al. (2017) meta-analysis with a PRISMA Score= 18/27 (17, 20). All the above are displayed in Table 6.

Moreover, regarding the items of PRISMA checklist, ten of them were reported in every study. These items belonged one to the Introduction Section, four to the Methods, three to the Results and two to Discussion (Items 3, 7, 12, 13, 14, 17, 18, 20, 24, 25, Score 100%). On the contrary, Objectives was the domain with the poorest adherence (Score= 20%), following Protocol & Registration and Search with 26, 7% adherence with PRISMA. Although Objectives was included in every meta-analysis, very few of them were presented according to PRISMA explanation and elaboration. Table 7 & Chart 4 display the reporting proportion of each domain. The items with the greatest adherence are highlighted and the others with the poorest are underlined

Table 6: The PRISMA Score of each meta-analysis

Author	*PRISMA SCORE Frequency*	*%*
Mattos	21/27	77
Nassar Jr	19/27	70
Hiremath	20/27	74
➡ *Israelsen*	24/27	88
➡ *Sagi*	17/27	62
Wang	23/27	85
Gluud 12'	21/27	77
Dobre	21/27	77
Facciorusso	23/27	85
Gifford	21/27	77
Gluud	20/27	74
Nanda	22/27	81
➡ *Zheng*	18/27	66
Allegretti	23/27	85
➡ *Sridharan*	24/27	88

Section	n	Item	% Percentage of "Yes"
TITLE	1	Title	80
ABSTRACT	2	Structured Summary	46,7
INTRODUCTION	3	Rationale	100
	4	Objectives	20
METHODS	5	Protocol & Registration	26,7
	6	Eligibility Criteria	73,3
	7	Information Sources	100
	8	Search	26,7
	9	Study Selection	80
	10	Data collection progress	73,3
	11	Data Items	86,7
	12	Risk of Bias in individual studies	100
	13	Summary Measures	100
	14	Synthesis of Results	100
	15	Risk Bias across studies	79,9
	16	Additional Analyses	86,7
RESULTS	17	Study Selection	100
	18	Study Characteristics	100
	19	Risk of Bias Within studies	80
	20	Results of Individuals studies	100
	21	Synthesis of Results	93,9
	22	Risk of Bias across studies	33,3
	23	Additional Analysis	86,7
DISCUSSION	24	SummaryEvidence	100
	25	Limitations	100
	26	Conclusions	93,3
FUNDING	27	Funding	60

Table 7: Reporting proportion of each PRISMA item

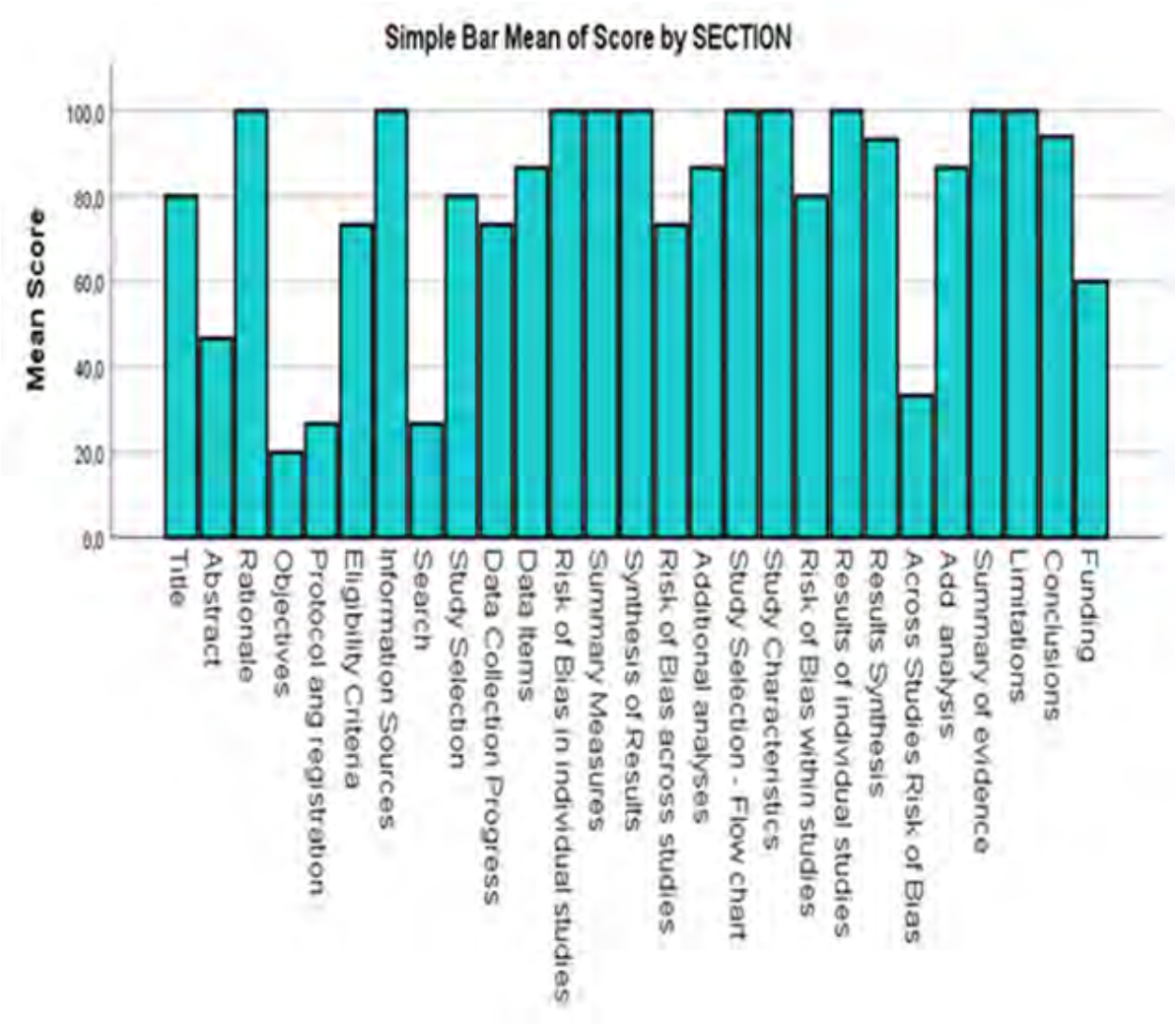

Chart 4: Reporting Proportion of each PRISMA item

Association of variables and study quality

JIF, Year of publication, the number of Authors and the number of Studies included in meta-analysis were considered as potential factors affecting the reporting quality. This potential correlation was examined using the correlation coefficient "r.(21) As it emerges from the aforementioned analysis, there is a statistically significant moderate positive correlation between reporting quality of meta-analysis considering PRISMA Score and the Year of publication (r = 0,558) (Chart 5), meaning that the most recently published meta-analyses have greater reporting quality than the older ones. Additionally, there is also a statistically significant moderate positive correlation between PRISMA Score and the included number of studies (RCT'S) with r = 0,617. This indicates that meta-analyses with larger sample size have greater Quality. (Chart 6).

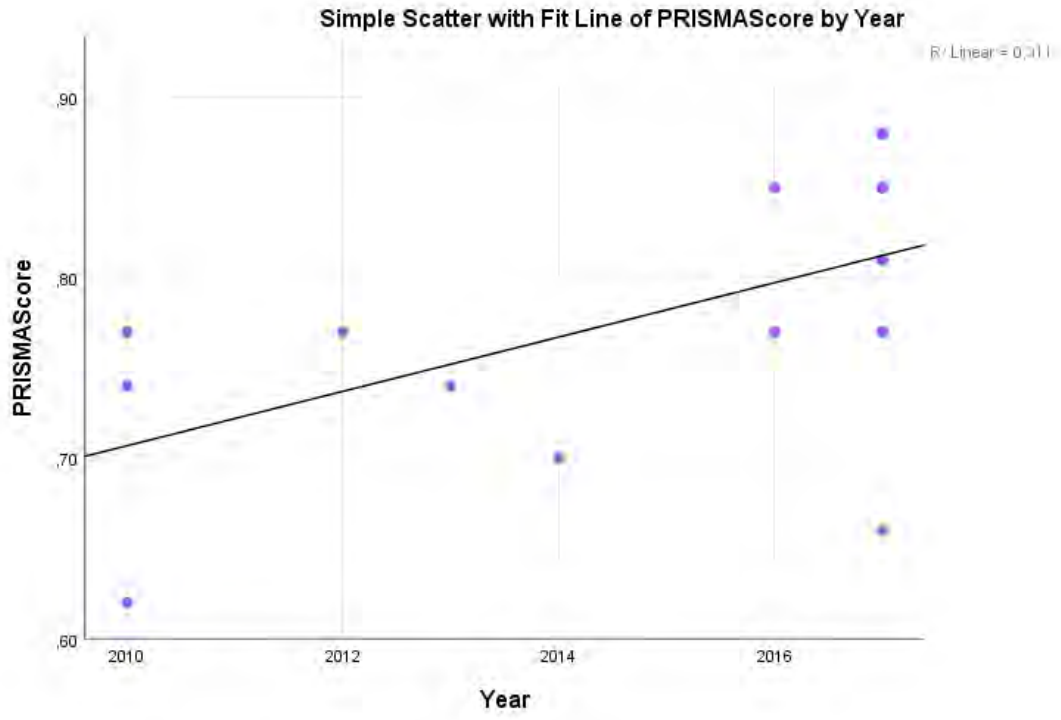

Chart 5: Scatter plot of PRISMA Score in comparison with Year of Publication.

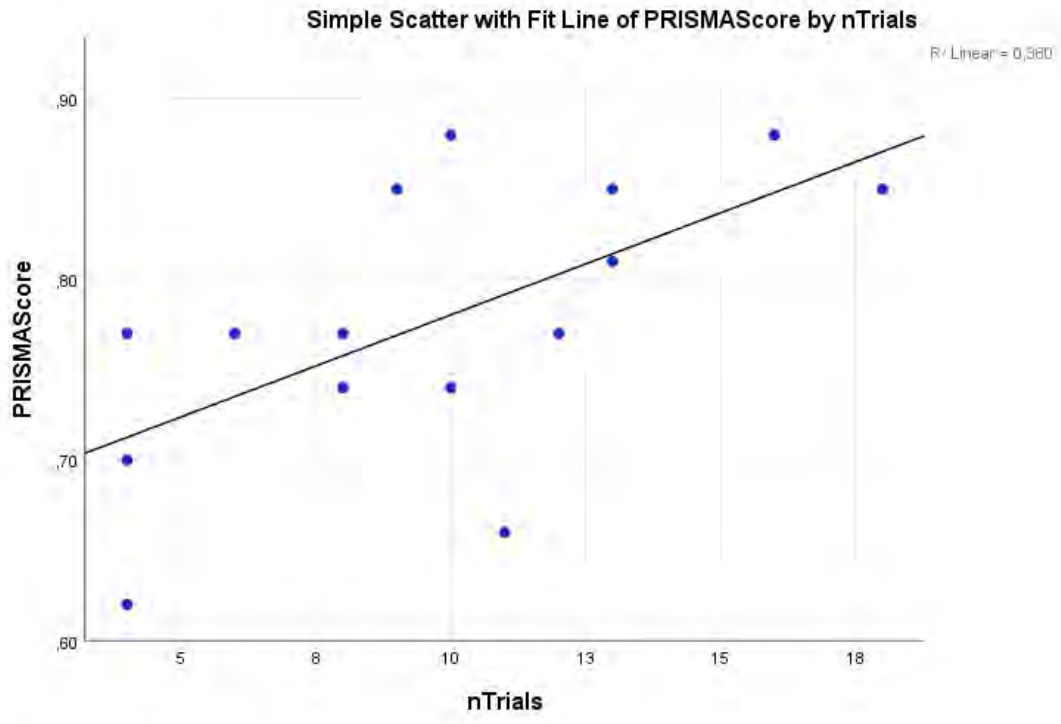

Chart 6: Scatter plot of PRISMA Score in comparison with number of RCT'S

Finally, the analysis proved a negligible correlation between Reporting Quality of meta-analysis and the Journal's Impact Factor (r = 0,279) and number of Authors (r = 0,111). Below Scatter Plots between PRISMA Score and JIF, number of Authors are also presented. (Chart 7&8) (The interpretation of Pearson Correlation is based on MM Mukaka 2012 (22)).

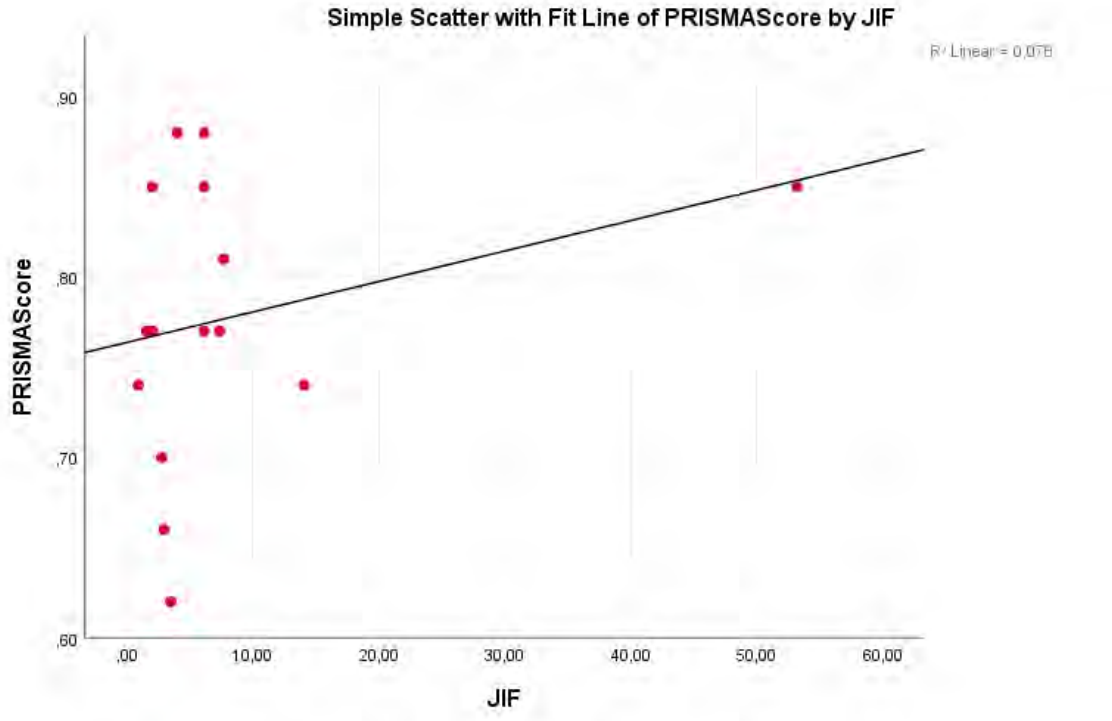

Chart 7: Scatter plot of PRISMA Score and JIF

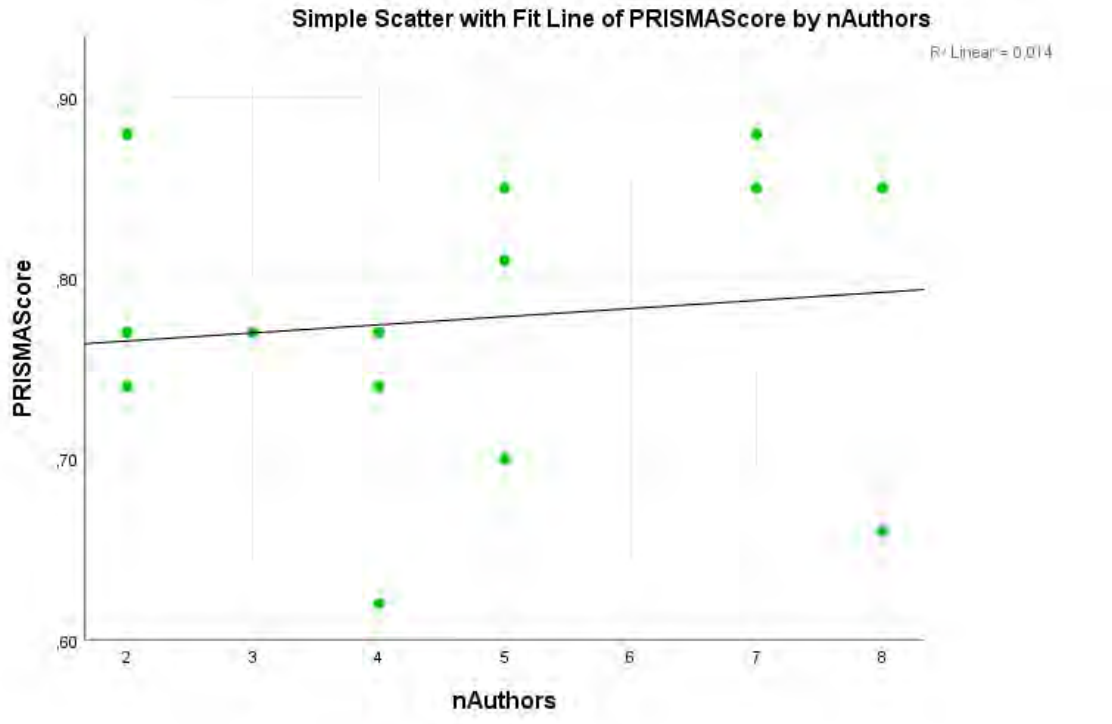

Chart 8: Scatter Plot of PRISMA Score - number of Authors

A potential association between reporting PRISMA Score and publication in PRISMA Endorsement Journal was examined as well. The existence of possible statistically significant difference in Quality Reporting was tested using T-test. From the analysis occurred that there is not a statistically significant difference in Quality Reporting regarding PRISMA Endorsement (Table 8). Likewise, the relation between Reporting Quality and meta-analyses supported by Cochrane Collaboration was tested and found no statistically significant difference. (Table 9)

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
PRISMAScore	Equal variances assumed	,073	,792	,664	13	,518	,03091	,04657	-,06969	,13151
	Equal variances not assumed			,656	5,250	,540	,03091	,04714	-,08854	,15036

Table 8: T - test for PRISMA Score and PRISMA Endorsement Journals

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
PRISMAScore	Equal variances assumed	,356	,561	1,440	13	,174	,07000	,04861	-,03502	,17502
	Equal variances not assumed			1,757	4,169	,151	,07000	,03984	-,03887	,17887

Table 9: T - test for PRISMA Score and Cochrane's Meta-analyses

A possible connection between Reporting Quality of a study and its studied Treatment comparisons was also examined, using One Way ANOVA and Post Hoc analysis. (4). Table 12 displays the results of the analysis. Five meta-analyses compared Terlipressin Vs Placebo, two Vs Noradrenaline, four Vs Placebo or Noradrenaline and four Vs Placebo or other vasoactive agents. Treatment Comparison was divided into four groups:

- Group 1: Terlipressin Vs Placebo or Albumin or No intervention/Observation
- Group 2: Terlipressin Vs Noradrenaline
- Group 3: Terlipressin Vs Placebo or Noradrenaline
- Group 4 : Terlipressin Vs Placebo or other Vasoactive agents

There was not proved difference in Reporting Quality regarding Treatment Comparisons of meta-analysis.

ANOVA

PRISMAScore

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	,016	3	,005	,831	,504
Within Groups	,070	11	,006		
Total	,085	14			

Table 10: One Way ANOVA for PRISMA Score and Treatment Comparisons

Post Hoc Tests

Multiple Comparisons

Dependent Variable: PRISMAScore

Bonferroni

(I) Comparison	(J) Comparison	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
1	2	,03700	,06660	1,000	-,1767	,2507
	3	,01700	,05340	1,000	-,1543	,1883
	4	-,05550	,05340	1,000	-,2268	,1158
2	1	-,03700	,06660	1,000	-,2507	,1767
	3	-,02000	,06894	1,000	-,2412	,2012
	4	-,09250	,06894	1,000	-,3137	,1287
3	1	-,01700	,05340	1,000	-,1883	,1543
	2	,02000	,06894	1,000	-,2012	,2412
	4	-,07250	,05629	1,000	-,2531	,1081
4	1	,05550	,05340	1,000	-,1158	,2268
	2	,09250	,06894	1,000	-,1287	,3137
	3	,07250	,05629	1,000	-,1081	,2531

Table 11: Post Hoc Comparisons of Groups of Treatment Comparisons

Variable	Pearson's R	Correlation[1]	P – Value	Significance
JIF	0,279	Negligible	0,313	No
Year	0,558	Moderate Positive	0,031	Yes
n Authors	0,111	Negligible	0,674	No
n Trials	0,617	Moderate Positive	0,014	Yes
PRISMA Endorsement *	-	-	0,518	No
Cochrane *	-	-	0,174	No
Treatment Comparison**	-	-	0,504	No

Table 12: Correlates of the reporting quality of meta-analysis regarding PRISMA Score and individual methodologic aspects

[1]: according to "MM Mukaka 2012 "* t-test analysis **One-Way ANOVA analysis

Clinical Outcomes

Nine of the meta-analyses reported in their analysis as outcome the resolution of HRS, comparing Terlipressin ± albumin with placebo ± albumin. Summarizing the outcomes of these meta-analyses it occurs that Terlipressin is almost 4-times superior to placebo or no treatment or albumin regarding the reversal of Hepatorenal Syndrome. Six out of nine studies report statistically significant difference and in the others p value is not stated. The Heterogeneity of the included studies of the meta-analyses range between 0- 70 %. In Table 13 OR, 95% CI, Overall Effect Z & P – value of each study are presented.

Author	OR	95% CI LL	95%CI UL	Heterogeneity (I^2)	Overall Effect (Z)	P- Value
Sagi (2010)	3,66	2,15	6,23	0	4,78	,00001
Wang (2017)	4,69	2,23	11,00	57	3,93	,00010
Dobre (2010)	7,47	3,17	17,59	24	4,60	,00001
Gifford (2017)	2,54	1,51	4,26	52	3,52	,00040
Nanda (2017)	4,72	1,72	12,93	70	N/S	,00300
Zheng (2017)	,24	,07	,65	N/S	N/S	
Sridharan (2017)	6,70	2,10	21,30	N/S	N/S	
Gluud (2010)	3,76	2,21	6,39	0	N/S*	
Facciorusso (2016)	4,48	1,88	10,67	60	3,38	,00070

Table 13: Terlipressin Vs Placebo regarding HRS Reversal. Outcomes of each meta-analysis * N/S: Not Stated

The Forest Plot (Chart 9) below depicts the OR (95%CI) of Terlipressin Vs Placebo considering the HRS Reversal of each study.

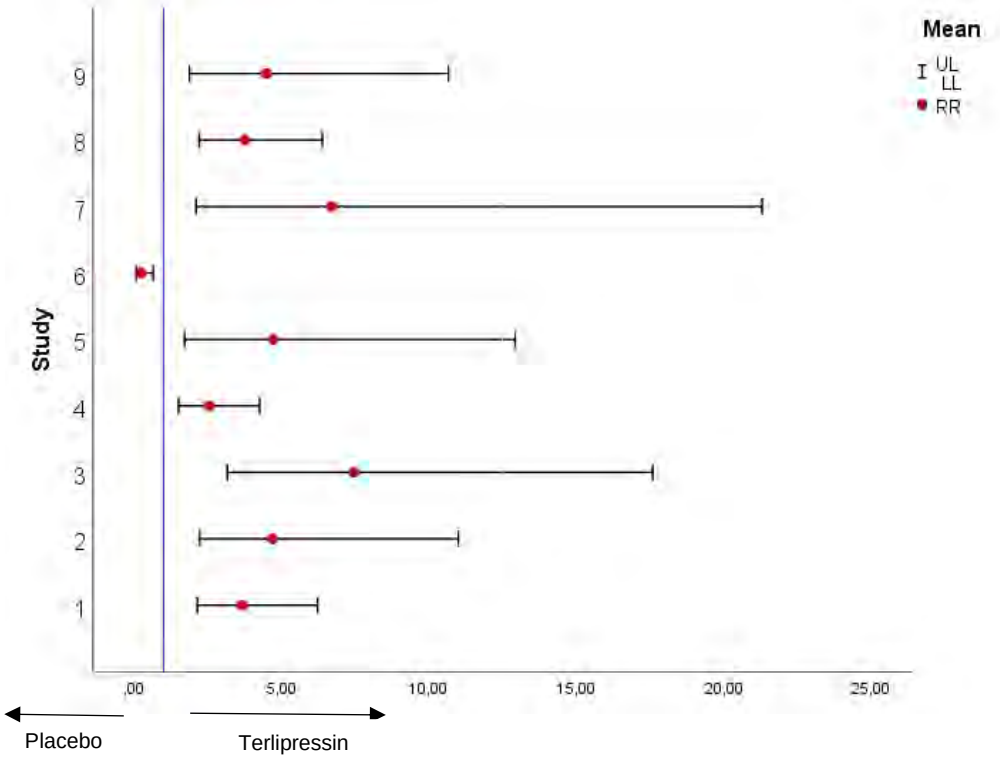

Chart 9: Terlipressin Vs Placebo considering the HRS Reversal of each study

Eight of the meta-analyses compared Terlipressin Vs Noradrenaline for the resolution of HRS in their analysis. None of them proved superiority of the one treatment in comparison with the other in terms of HRS remission. The included studies of meta-analyses had no Heterogeneity. All the above are displayed in table 14 and Chart 10.

Author	OR	95% CI LL	95%CI UL	Heterogeneity (I^2)	Overall Effect (Z)	P- Value
Nassar (2014)	,97	,76	1,23	0	N/S*	,79
Wang (2017)	1,01	,65	1,57	0	,05	,96
Dobre (2010)	1,23	,43	3,54	0	,30	,70
Gifford (2017)	,99	,67	1,45	N/S*	N/S*	N/S*
Nanda (2017)	,91	,46	1,79	0	N/S*	N/S*
Zheng (2017)	,97	,25	3,73	N/S*	N/S*	N/S*
Mattos (2016)	1,03	,81	1,31	0	,25	,80
Facciorusso (2016)	,89	,47	1,69	0	,36	,72

* N/S: Not Stated

Table 14: Terlipressin Vs Noradrenaline regarding HRS Reversal. Outcomes of each meta-analysis

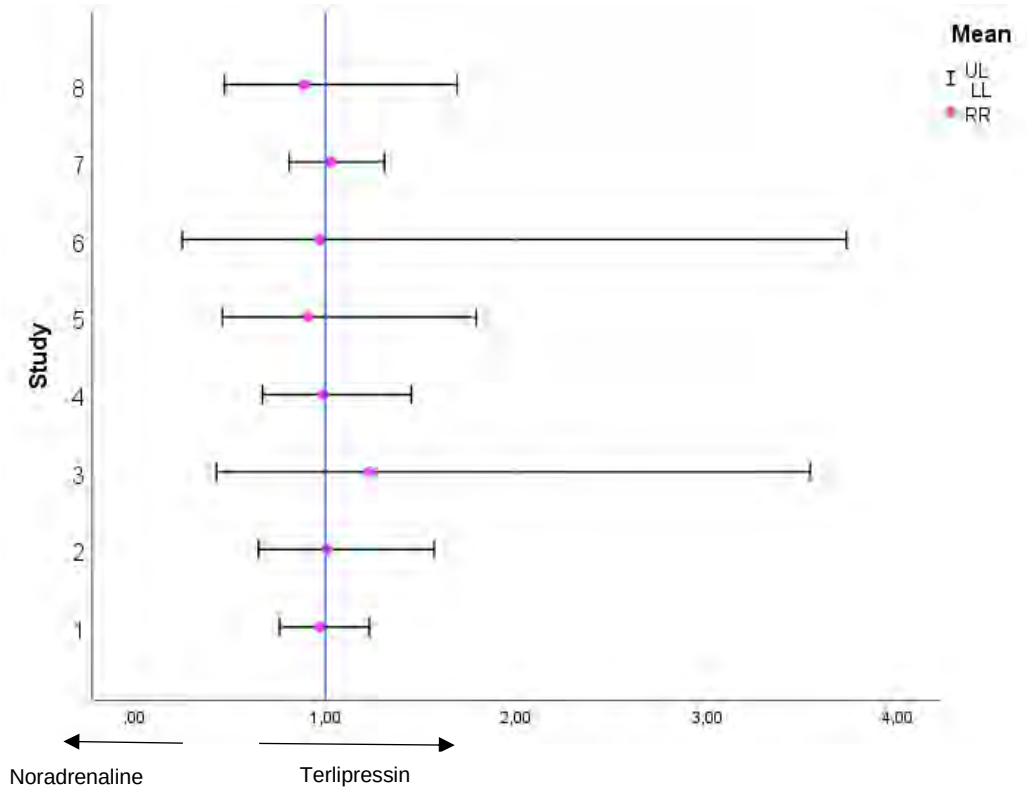

Chart 10: Terlipressin Vs Noradrenaline considering the HRS Reversal of each study

Moreover, six meta-analyses studied the occurrence of serious Adverse Events and especially the occurrence of cardiovascular events presented with Terlipressin or Placebo. As it appears, Terlipressin is associated with higher risk of serious Adverse Events in relation with Placebo or Albumin or Observation. (Table 15 & Chart 11)

Author	OR	95% CI LL	95%CI UL	Heterogeneity (I^2)	Overall Effect (Z)	P- Value
Gluud (2012)	7,26	1,70	31,05	0	2,67	,007
Wang (2017)	1,57	,63	3,93	4	2,75	,006
Gifford (2017)	3,56	1,64	7,72	0	3,21	,001
Gluud (2010)	9,00	2,14	37,85	0	N/S*	N/S*
Sridharan (2017)	7,40	1,90	28,90	N/S*	N/S*	N/S*
Allegretti (2017)	7,26	1,70	31,50	0	2,60	,007

* N/S: Not Stated

Table 15: Terlipressin Vs Placebo regarding Adverse Events

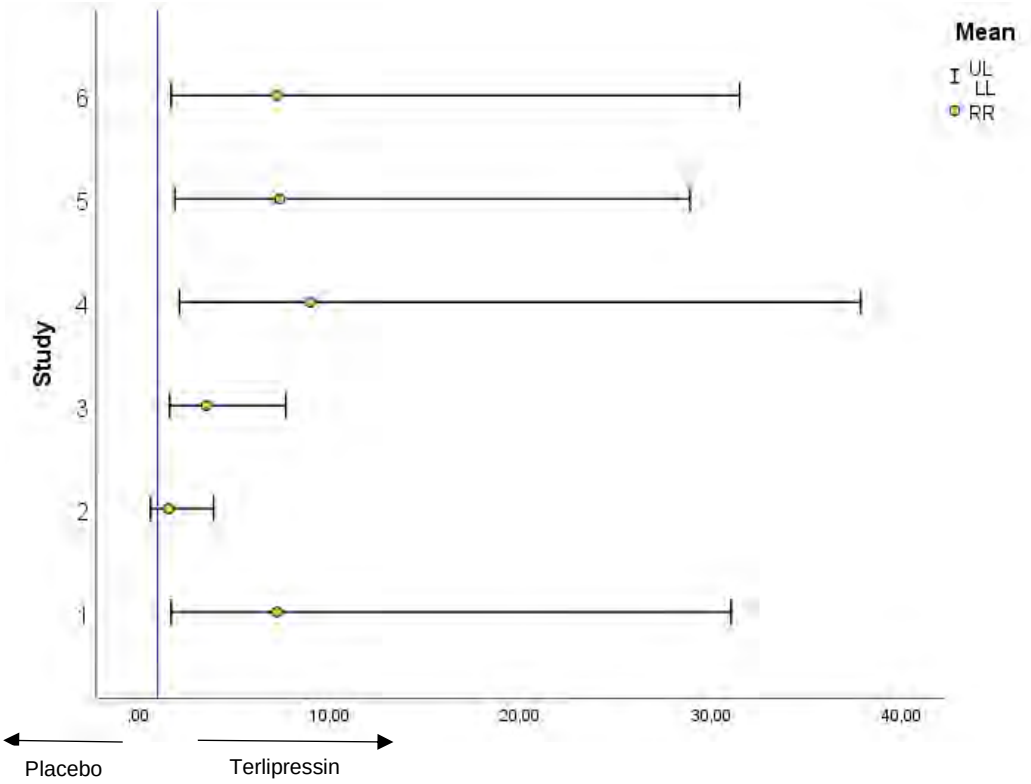

Chart 11: Terlipressin Vs Placebo regarding Adverse Events

Finally, two meta-analyses (*Gifford, 2017* & *Sridharan, 2017*) (9, 18) studied the efficacy of bolus terlipressin administration Vs continuous infusion of Terlipressin, regarding the remission of HRS. According to these studies, continuous infusion is associated with higher reversal rates than bolus administration. Specifically RR= 1, 22 95% CI (0, 77 – 1, 97) and RR = 9, 9 95% CI (2, 2 – 44, 2) respectively.

Discussion

Hepatorenal syndrome is a serious complication of decompensated liver disease, with rapid progression. HRS can lead to multiple organ failure if left untreated. Although the best treatment of choice is liver transplantation, several pharmacological agents are being used in order to ameliorate renal function and reverse the syndrome. The most studied and widely used agent is Terlipressin. As there are no universal guidelines regarding treatment of Hepatorenal syndrome, many meta-analyses, and systematic reviews have been published the last decade in order to compare the efficacy and safety of Terlipressin in comparison with placebo or other vasoconstrictor drugs. Meta-analyses and systematic reviews comprise important tools, which can provide high-quality evidence and can lead to essential conclusions.

In the present review, 15 meta-analyses being published from 2010 to 2018 were identified and were evaluated using the PRISMA Statement's checklist. The overall reporting quality of the existing meta-analyses is considered moderate with an average adherence rate of all items to the checklist being 77, 7%. Ten items of the checklist, which belonged mainly in sections of Methods & Results, were reported in all meta-analyses. Most of the meta-analyses reported inadequately their Objectives, resulting in low rates of PRISMA compliance.

PRISMA Score was considered as the value which represents the Quality of each study. Correlation analysis was performed and showed a moderate positive correlation between PRISMA Score and Year of Publication and also the number of trials included in meta-analyses. There was no evidence of association regarding the reporting quality of meta-analyses and the JIF or PRISMA endorsement of the Journal being published. Also, Cochrane Systematic reviews were not of higher reporting quality.

Regarding the outcomes of the meta-analyses, most of them compared the efficacy of terlipressin vs placebo in reversal of HRS. Terlipressin was in all of them superior to placebo almost 4-times. On the other hand, Terlipressin was associated with more and more serious adverse events than placebo. Eight of the meta-analyses compared the efficacy of Terlipressin vs Noradrenaline in reversal of HRS. None of them proved superiority or inferiority of the one drug over the other. Also, they were associated with equal number of adverse events. Noradrenaline was related with more cardiovascular events in comparison with Terlipressin that was related mostly to abdominal events, as pain or diarrhea.

Some limitations exist in the present study. The literature search was confined to electronic databases and there were language and time restriction. Compliance of the found meta-analyses with the inclusion criteria and their adherence to the PRISMA checklist was evaluated by only one author. The included studies were assessed only by PRISMA Statement, which is a tool of reporting only quality. In order for this review to be fully featured, the eligible studies should also have been assessed using methodological tools as AMSTAR Score.

Moreover, PRISMA Score was considered as value symbolizing quality in general of the meta-analysis. Regarding content, the meta-analyses included in this review were significantly heterogeneous. To begin with, five of the meta-analyses studied only patients with Type 1 Hepatorenal Syndrome and the in the remaining the percentage of HRS 1 and HRS 2 populations varied. Furthermore, the majority of meta-analyses were based on RCT'S with low to moderate quality and have high risk of bias. So a try to draw conclusions based on these studies will be risky.

In conclusion, the last decade many meta-analyses, of moderate reporting quality according to PRISMA Statement, have been published studying the efficacy of Terlipressin in Hepatorenal syndrome. This review presented the strengths and weaknesses of these studies regarding their reporting quality and proved that the most recently published meta-analyses and those which include a larger amount of RCT's are of higher quality. Some limitations exist mainly in literature search and in the great heterogeneity of the meta-analyses. Further studies of equivalence between Terlipressin and Noradrenaline should be performed. Finally, further reviews should include more meta-analyses and assess their quality with more than one tool in order general conclusions of treatment of Hepatorenal syndrome to be drawn.

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